

Pharmacokinetics of Imipenem-Cilastatin in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration

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The pharmacokinetics of imipenem-cilastatin were investigated in 12 critically ill patients with acute renal failure (ARF) managed by continuous veno-venous hemofiltration (CVVH) while receiving a fixed combination of 500 mg of imipenem-cilastatin intravenously three or four times daily. No adverse drug reactions were observed. Plasma and hemofiltrate samples were taken at specified times during one dosing interval, and the concentrations of imipenem and cilastatin were determined by high-performance liquid chromatography. Pharmacokinetic variables were calculated by a first-order, two-compartment pharmacokinetic model for both substances. Total clearances of imipenem and cilastatin (mean \pm standard deviations) were 122.2 ± 28.6 and 29.2 ± 13.7 ml/min, respectively, with hemofiltration clearances of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively. Mean imipenem dosage requirements were approximately 2,000 mg/24 h ($2,111.8 \pm 493.4$ mg/24 h). They were calculated in order to achieve an average steady-state concentration of 12 mg/liter to ensure that concentrations in plasma exceeded the MICs at which 90% of intermediately resistant bacteria are inhibited (8 mg/liter) during the majority of the dosing interval. By contrast, the recommended dosage for patients with end-stage renal failure (ESRF) and infections caused by intermediately resistant bacteria is 1,000 mg/24 h. This remarkable difference may be due (i) to differences in the nonrenal clearance of imipenem between patients with ARF and ESRF and (ii) to the additional clearance by the hemofilter. Since the total clearance of cilastatin was low, marked accumulation occurred, and this was particularly pronounced in patients with additional liver dysfunction. Thus, in patients with ARF managed by CVVH, rather high imipenem doses are required, and these inevitably result in a marked accumulation of cilastatin. The doses of imipenem recommended for patients with ESRF, however, will lead to underdosing and inadequate antibiotic therapy.

Imipenem is a carbapenem antibiotic with a broad spectrum of activity against many common pathogens (6) and is thus particularly useful for critically ill patients with septic complications due to unidentified bacteria or bacteria resistant to many other antibiotics. Imipenem is rapidly metabolized by the renal brush border enzyme dehydropeptidase I (DHP I). It is therefore coadministered as a one-to-one combination with the DHP I inhibitor cilastatin, which results in the excretion of about 70% of unchanged imipenem into the urine (25) and a reduction in renal toxicity (18). In healthy volunteers and patients with normal renal function, both agents have almost identical pharmacokinetic properties (8, 9, 26). In patients with renal insufficiency (acute renal failure [ARF] and end-stage renal failure [ESRF]), however, the elimination of both drugs is differently affected, resulting in a much higher accumulation of cilastatin (11). Furthermore, in patients with ESRF total imipenem clearance is more reduced than that in patients with ARF (23). Dose recommendations for patients with renal insufficiency are based mostly on the kinetic data obtained from patients with ESRF (11) undergoing either intermittent hemodialysis (3, 20) and hemofiltration (1) or continuous ambulatory peritoneal dialysis (30). Few data concerning adjustments of the imipenem-cilastatin dose in patients with ARF are available (23, 35), but ARF is a common complication in critically ill patients. The preferred device for renal replacement therapy

in patients with ARF is the pump-driven continuous veno-venous hemofiltration (CVVH), which allows a constant flow and a high replacement rate (20 to 30 liters/day) and is therefore more effective than the older method, continuous arterio-venous hemofiltration (CAVH), in removing urea nitrogen from the body. Since CAVH depends on the arteriovenous pressure gradient, it may not function optimally in patients with hypotonic episodes or shock (31, 34). Thus, clearance data obtained for certain drugs during CAVH (4, 12, 19, 27, 35) cannot be readily applied to patients undergoing CVVH. The aim of the present study, therefore, was (i) to evaluate the pharmacokinetics of imipenem and cilastatin in patients with ARF undergoing CVVH and (ii) to give practical dosing recommendations applicable to these patients.

MATERIALS AND METHODS

Patients. Thirteen consecutive patients who were admitted to the surgical intensive care unit, who were treated with CVVH for ARF, and who were receiving imipenem-cilastatin (Zienam; Merck Sharp & Dohme, Haar, Germany) for the treatment of a severe life-threatening infection were enrolled in this study. One patient had to be excluded because hemofiltration was interrupted during the collection interval. Patient characteristics and diagnoses are presented in Table 1. Except for patients 1 and 5 (diuresis, 600 ml/24 h), urine production was <150 ml/24 h (Table 1). Patients 4 and 6 had a documented preexisting moderate reduction in renal function. The hemofiltrate creatinine concentrations ($C_{\text{crea-HF}}$) were measured by photometric determinations of the Jaffé reaction by using the Merckotest (Merck, Darmstadt, Germany) reagent kit. The hemofiltration creatinine clearance (HF-CL_{CR}) was determined as $\text{HF-CL}_{\text{CR}} = C_{\text{crea-HF}} \times V_{\text{HF}} / C_{\text{crea-serum}} \times t$, V_{HF} is the hemofiltrate volume, $C_{\text{crea-serum}}$ is the serum creatinine concentration, and t is the collection time. Because in the 10 anuric patients renal creatinine clearance (CL_{CR}) was approximately zero, HF-CL_{CR} is approximately equal to the total CL_{CR} in these patients.

The total CL_{CR} for the two patients with residual renal function was calculated

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TABLE 1. Characteristics of 12 critically ill patients with ARF treated by CVVH and with imipenem-cilastatin as a fixed combination

Patient no.	Age (yr)	Sex ^a	Urine output/ 8 h (ml)	HF-CL _{CR} (ml/min)	Imipenem dosage (mg/24 h)		Liver function	Diagnosis or surgery
					Maximal recommended	Calculated		
1	37	m	200	18.3/60.8 ^b	2,250	2,989.4	B	Liver transplantation
2	60	m	0	16.3	1,000	1,728.0	A	Laryngectomy and hypopharyngectomy
3	54	m	0	28.4	2,000	1,900.8	B	Liver transplantation
4	76	m	10	16.0	1,000	1,252.8	A	Coronary heart disease, bypass surgery
5	63	f	200	18.4/61.3 ^b	2,250	2,263.7	A	Aortic and tricuspid valve replacement
6	70	m	50	19.2	1,000	2,471.0	A	Coronary heart disease, bypass surgery
7	66	m	0	15.2	1,000	1,797.1	A	Coronary heart disease, bypass surgery
8	78	m	0	11.5	1,000	2,298.2	A	Retroperitoneal abscess
9	78	m	0	17.1	1,000	1,987.2	A	Hip arthroplasty and iliopsoas muscle abscess
10	69	f	0	20.2	1,000	1,831.7	B	Aortic valve replacement and bypass surgery
11	69	m	20	19.8	1,000	1,952.6	B	Acute duodenal ulcer bleeding, abdominal surgery
12	67	m	0	19.8	1,000	2,868.5	B	Arterial occlusive disease with amputation at the thigh

^a m, male; f, female.^b Total CL_{CR} calculated from serum creatinine levels.

by the method of Jelliffe and Jelliffe (17), which is suitable for calculating the CL_{CR} in the case of an instable kidney function. HF-CL_{CR} values are depicted in Table 1.

Concomitant drug therapy consisted mainly of antibiotics ($n = 13$ patients), digitoxin ($n = 9$), intravenous catecholamines ($n = 8$), opioids ($n = 8$) ranitidine ($n = 7$), midazolam ($n = 5$), sucralfate ($n = 3$), and nonopioid analgesics ($n = 3$). The study was approved by the institutional Ethics Review Board.

CVVH. Vascular access was obtained through the subclavian vein with a double-lumen catheter (Mahurkar Catheter Set; Quinton Instrument Co., Bothwell, Wash.). The extracorporeal circuit was set up by dialysis nurses and was changed every 48 h or if hemofilter clotting was present. CVVH was accomplished with a hollow-fiber high-flux hemofilter (Filtral 10G; Hospal, France) with polyacrylonitrile membranes (AN69 HF; Hospal). The blood flow rate was 150 to 170 ml/min. The filtration rate was adjusted to 1.1 to 1.2 liters/h with a replacement rate of 1 liter/h resulting in an ultrafiltration rate of 100 to 200 ml/h.

Sample collection. During CVVH patients received 500 mg of each of imipenem and cilastatin either three or four times daily ($n = 6$ in each group). After starting the therapy with imipenem-cilastatin, we waited at least 3 days before starting sample collection in order to achieve steady-state concentrations of the drugs. Plasma and hemofiltrate sampling was started after the CVVH system was operating at the desired pump speed for at least 30 min. The drug combination dissolved in 50 ml of normal saline was infused into a central venous catheter over a period of 30 min with an infusion pump. Blood samples (3.2 ml, using EDTA as anticoagulant) were obtained from an arterial catheter immediately before dosing and at 0.6, 1, 1.5, 2, 4, 6, and 8 h after starting the infusion. Simultaneously, hemofiltrate samples were taken and the volume filtered over the time interval was measured. Since imipenem is hydrolyzed rapidly in hemofiltrate (and plasma) and imipenem hydrolysis is dependent on the pH (29), 0.5 M MOPS (morpholinopropanesulfonate; Aldrich, Steinheim, Germany) buffer (pH 6.8) was used as a stabilizer as described previously (1) and was added to the filtrate collecting tank at a concentration of 1:20 prior to the collection period. MOPS buffer provided for the stability of imipenem for at least 4 h at room temperature, as tested before the actual study was started. Blood was immediately centrifuged ($2,000 \times g$, 10 min, 4°C), and aliquots of plasma samples were mixed 1:1 with 0.5 M MES (morpholinoethanesulfonate; Aldrich) buffer (pH 6.0). Plasma and hemofiltrate samples were stored at -70°C until analysis, which was performed on the same day or the next day in order to adjust the dose for the individual patient.

Drug assay. Plasma and hemofiltrate samples were prepared and analyzed by high-performance liquid chromatography (HPLC) by the methods of Gravallese et al. (13) (imipenem) and Myers and Blumer (24) (cilastatin), with some minor modifications. Imipenem and cilastatin were provided by Merck Sharp & Dohme, West Point, Pa. The HPLC system consisted of a Beckman 114 pump (Beckman, Munich, Germany), a model SP 100 UV monitor (Spectra Physics, Darmstadt, Germany) fitted with a model 231 autosampler (Abimed, Langenfeld, Germany), and a CR3A integrator (Shimadzu, Egling, Germany).

All plasma samples were diluted 1:1 with MES buffer directly after centrifugation of the EDTA-anticoagulated blood as mentioned above. Plasma samples were deproteinized by using Centrifree ultrafilters (Amicon, Witten, Germany) with centrifugation at $2,000 \times g$ and 4°C for 1 h (imipenem) or proteins were precipitated with 80% acetonitrile (Merck, Frankfurt, Germany) and 20% perchloric acid and centrifuged at $15 \times g$ for 5 min (cilastatin). Plasma samples used for cilastatin concentration determination were prediluted 1:5 with 0.1 M potassium phosphate (pH 2.5; Sigma) prior to precipitation with perchloric acid, which was performed by adding 50 µl of perchloric acid to 200 µl of plasma prediluted 1:10. The prepared samples and the hemofiltrate samples were analyzed by direct

injection of 100 µl onto the HPLC system. Chromatography was performed on a reversed-phase Nucleosil C₁₈ column (120 mm by 4 mm [inner diameter]; Macherey Nagel, Düren, Germany). The mobile phase for imipenem consisted of 0.2 M boric acid (pH 7.2); that for cilastatin was 8% acetonitrile in 0.1 M potassium phosphate (pH 2.5). Flow rates were 1 ml/min. Peak detection was accomplished with a UV detector (Spectra 100; Spectra Physics, Darmstadt, Germany) set at 298 nm for imipenem and 220 nm for cilastatin.

The recovery of imipenem from plasma and hemofiltrate was approximately 100%; that of cilastatin was 78% from plasma and approximately 100% from hemofiltrate. The intraday coefficients of variation for the concentrations 5, 10, and 15 mg/liter were <0.4 and <4% for imipenem and cilastatin, respectively. The interday coefficients of variation for the same concentrations were <4% (imipenem) and <2% (cilastatin). The lower limit of quantification for imipenem was 0.125 mg/liter in plasma and 0.06 mg/liter in hemofiltrate. The corresponding values for cilastatin were 0.06 mg/liter.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed by using TOPFIT software (14) on an International Business Machines-compatible computer. One- and two-compartment open models were tested to describe the plasma concentration-time profiles of imipenem and cilastatin, and the two-compartment open model was judged to be optimal by the Akaike (36) and Imbimbo et al. (16) information criteria for both drugs. The total area under the concentration-versus-time-curve (AUC) and the area under the first moment curve were calculated by the linear trapezoidal rule. The total body clearance (CL) was obtained by the equation $CL = \text{dose}/AUC$. The sieving coefficient (Sc) was calculated as $Sc = C_{HF}/C_{PI}$, where C_{HF} is the concentration of the drug in the hemofiltrate and C_{PI} is the corresponding concentration in plasma.

The hemofiltration clearances (CL_{HF}s) of imipenem and cilastatin were calculated by using the following equations: $CL_{HF} = C_{HF} \times V_{HF}/C_{PI} \times t$ (equation 1) and $CL_{HF} = AUC_{HF} \times Q_{HF}/AUC_{PI}$ (equation 2), where V_{HF} is the volume of the hemofiltrate, t is the time interval, AUC_{HF} is the area under the hemofiltrate concentration-versus-time curve, AUC_{PI} is the area under the plasma concentration-versus-time curve, and Q_{HF} is the preset hemofiltrate flow rate. By using equation 1, a clearance value for each time interval was obtained, and the mean value for sampling points 3 to 8 was used as the overall CL_{HF} value.

The total amount of the drug eliminated by hemofiltration (X_{HF}) was calculated as $X_{HF} = AUC_{HF} \times Q_{HF}$. Since in 10 of 12 patients the renal clearance was negligible, the nonrenal clearance (CL_{NR}) was obtained by the relationship $CL = CL_{NR} + CL_{HF}$. In the two patients with residual renal function, CL_{NR} was not calculated. The average steady-state concentration (C_{SSav}) was calculated by the equation $C_{SSav} = \text{dose}/CL \times \tau$, where τ is the dosing interval. The clearance data derived for each patient were used to calculate an imipenem dosing regimen that maintained a C_{SSav} of 12 mg/liter by using the following equation: 24-h dose = $CL \times 12 \text{ mg/liter} \times 24 \text{ h}$, where CL is in liters per hour.

The 12-mg/liter C_{SSav} was chosen to ensure that the concentration in the plasma of the patient remained above the MIC at which 90% of isolates are inhibited (MIC₉₀; 8 mg/liter) for intermediately resistant *Pseudomonas aeruginosa* for the majority of the dosing interval. The 24-h dose of cilastatin was calculated correspondingly.

The total mean residence time (MRT) was calculated as $MRT = AUMC/AUC$, and the volume of distribution at steady state (V_{SS}) was obtained by $V_{SS} = MRT \times CL$.

Statistics. The estimated imipenem doses for 24 h were compared with the manufacturer's recommended doses for patients with reduced renal function. These recommended doses depend on CL_{CR}. For patients with a CL_{CR} of <20 ml/min, dosages of 500 to 1,000 mg/24 h are recommended. For patients with a CL_{CR} of 21 to 40 ml/min, 750 to 2,000 mg/24 h is the recommended dosage, and

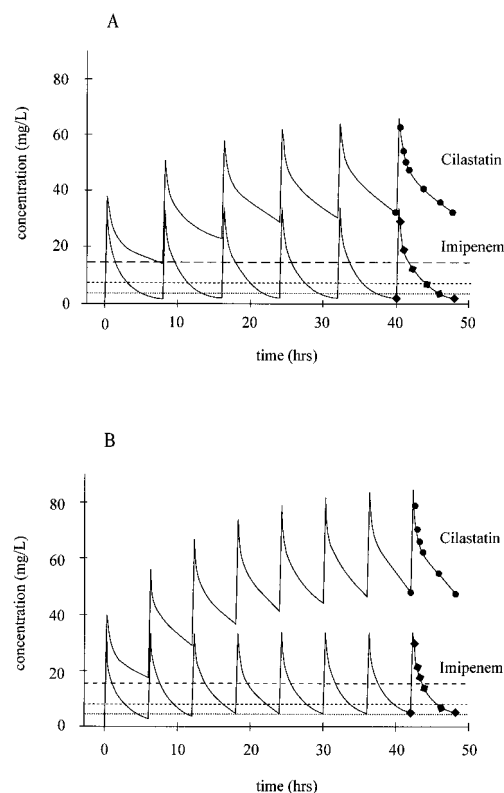


FIG. 1. Concentrations of imipenem and cilastatin in plasma of critically ill patients during continued intermittent application of equal doses (500 mg each). The patients suffered from ARF and were treated by CVVH. (A) Patients received 500 mg of imipenem and 500 mg of cilastatin every 8 h. (B) Patients received 500 mg of imipenem and 500 mg of cilastatin every 6 h. The MIC₉₀s for susceptible bacteria (.....; 4 mg/liter) intermediately resistant bacteria (-----; 8 mg/liter), and resistant bacteria (---; >16 mg/liter) are presented. Samples were collected during one interval after reaching steady-state levels. The concentrations of drugs in plasma are depicted as follows: ◆, imipenem; ●, cilastatin.

patients with a CL_{CR} of 41 to 70 ml/min should be treated with 1,000 to 2,250 mg/24 h (22). For the statistical analysis the highest recommended dosage for each patient according to the patient's CL_{CR} was used. The unpaired two-tailed Student's *t* test was applied, and a value of *P* of <0.05 was considered statistically significant. The AUC₀₋₈ of imipenem and cilastatin were examined for their correlation with total CL_{CR} by using the Pearson correlation coefficient. In order to find out if the CL of imipenem and the CL of cilastatin were dependent on the liver function (function A is normal or slightly elevated glutamic oxalacetic transaminase or glutamic pyruvic transaminase level; function B is markedly elevated total bilirubin level [> 8 mg/dl] plus one or more markedly impaired other liver function tests), the unpaired two-tailed Student's *t* test was applied and a *P* value of <0.05 was considered statistically significant. Data are expressed as means ± standard deviations (SDs).

RESULTS

Simulated plasma concentration-versus-time curves for imipenem and cilastatin during continued intermittent application of equal doses (500 mg of each of imipenem and cilastatin) are depicted in Fig. 1A and B for 8- and 6-h dosing intervals, respectively. Mean plasma and hemofiltrate concentration-versus-time curves for all patients obtained during the collection interval at steady state are depicted in Fig. 2A (8-h dosing interval) and Fig. 2B (6-h dosing interval). The mean CLs were 122.2 ± 28.6 and 29.2 ± 13.7 ml/min for imipenem and cilastatin, respectively, with CL_{HF}s of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances (CL_{NR}s) of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively (Table 2). After reaching the peak hemofiltrate concen-

tration 1 h after the start of the infusion, the *Sc* and the CL_{HF} were constant until the end of the dosing interval. Interestingly, 19.8% ± 5.7% of the CL of imipenem was provided by hemofiltration. The corresponding value for cilastatin was 65.2% ± 26.7%. The total amount of the drug eliminated by hemofiltration was calculated as 89.1 ± 26.0 mg (17.8% ± 5.2% of the dose) for imipenem and 303.2 ± 123.6 mg (60.6% ± 24.7% of the dose) for cilastatin. The terminal half-lives for imipenem and cilastatin were 2.9 ± 1.4 and 9.7 ± 4.4 h, respectively. The values of the pharmacokinetic parameters are summarized in Table 2. Since body weight and length are often not exactly known in intensive care unit patients, the pharmacokinetic parameters were not corrected for body mass.

The calculated total daily imipenem requirements in our patients with ARF (2,111.8 ± 493.4 mg) were significantly (*P* = 0.002) higher than the manufacturer's maximal recommended doses for patients with ESRF (1,409.1 ± 573.1 mg) and infections with intermediately resistant bacteria and with the corresponding CL_{CR} values. They greatly exceeded the recommended dosage of 500 to 1,000 mg/24 h for patients with CL_{CR}s of less than 20 ml/min, which can generally be assumed for anuric patients. Our patients received either 1,500 or 2,000 mg/24 h, but none of these patients experienced an adverse

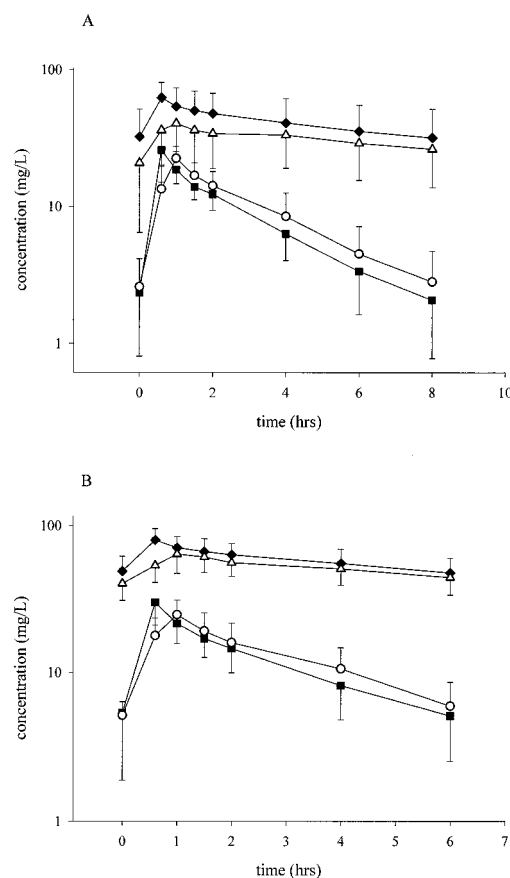


FIG. 2. Plasma and hemofiltrate concentration-versus-time curves for imipenem and cilastatin (mean ± SD) in critically ill patients with ARF treated by CVVH. The collection interval during steady state is depicted. A total of 500 mg of imipenem and 500 mg of cilastatin were dissolved in 50 ml of saline and were applied as a 30-min infusion. (A) Patients received 500 mg of imipenem and 500 mg of cilastatin every 8 h. (B) Patients received 500 mg of imipenem and 500 mg of cilastatin every 6 h. The drugs were administered at time zero. Symbols: ■, plasma imipenem concentration; ◆, plasma cilastatin concentration; ○, hemofiltrate imipenem concentration; △, hemofiltrate cilastatin concentration.

TABLE 2. Values of pharmacokinetic parameters for 12 critically ill patients with ARF following the administration of a fixed combination of 500 mg of each of imipenem and cilastatin either three or four times daily^a

Drug	CL (ml/min)	CL _{HF} (ml/min)	CL _{HF} (%)	X _{HF} (mg)	X _{HF} (%)	CL _{CR} (ml/min)	t _{1/2α} (h)	t _{1/2β} (h)	V _{ss} (liter)	MRT (h)	Sc	Calculated 24-h dose (mg)	C _{max} (mg/liter), at 0.5 g 4 times/day	C _{max} (mg/liter), at 0.5 g 3 times/day	C _{min} (mg/liter), at 0.5 g 4 times/day	C _{min} (mg/liter), at 0.5 g 3 times/day	C _{ssav} (mg/liter), at 0.5 g 4 times/day	C _{ssav} (mg/liter), at 0.5 g 3 times/day
Imipenem	122.2 ± 28.6	22.9 ± 2.5	19.7 ± 5.7	89.1 ± 26.0	17.8 ± 5.2	90.8 ± 26.3	0.28 ± 0.3	2.87 ± 1.4	24.3 ± 7.7	3.19 ± 1.1	1.2 ± 0.1	2,111.8 ± 493.4	30.2 ± 8.0	26.5 ± 4.9	4.1 ± 1.2	2.34 ± 1.4	12.4 ± 3.7	8.7 ± 1.7
Cilastatin	29.2 ± 13.7	16.1 ± 3.1	65.2 ± 26.7	303.2 ± 123.6	60.6 ± 24.7	13.2 ± 13.9	0.25 ± 0.3	9.73 ± 4.4	19.6 ± 7.3	13.45 ± 6.5	0.8 ± 0.2	504.9 ± 235.9	76.9 ± 16.2	61.5 ± 21.3	43.5 ± 15.4	30.1 ± 20.0	58.0 ± 15.9	43.1 ± 22.3

^a Values are means ± SDs. Abbreviations: CL, total plasma clearance; CL_{HF}, hemofiltration clearance; CL_{CR}, amount of drug eliminated by hemofiltration; CL_{NR}, nonrenal clearance; t_{1/2α}, half-life of the fast disposition phase; t_{1/2β}, terminal half-life of the slow disposition phase; V_{ss}, volume of distribution at steady state; MRT, mean residence time; Sc, sieving coefficient; calculated dose, dose needed for 24 h in order to reach a C_{ssav} of 12 mg/liter; C_{max}, measured peak concentration of drug in plasma; C_{min}, measured trough concentration of drug in plasma; C_{ssav}, average steady-state concentration.

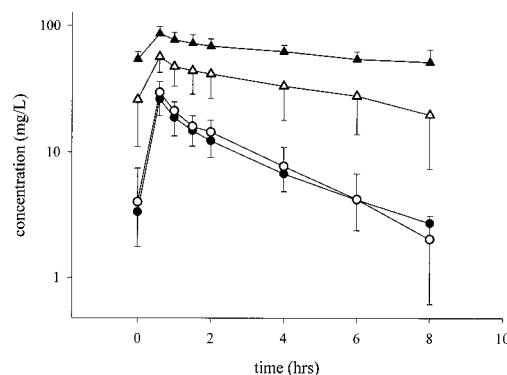


FIG. 3. Plasma concentration-versus-time curves of imipenem and cilastatin (mean ± SD) in critically ill patients with ARF with and without additional liver dysfunction. Liver dysfunction was assumed if patients had markedly elevated bilirubin levels (>8 mg/dl) plus one or more other remarkably affected liver function tests (three times greater than the normal value). Symbols: ○, plasma imipenem concentration in patients with normal liver function; ●, plasma imipenem concentration in patients with liver dysfunction; △, plasma cilastatin concentration in patients with normal liver function; ▲, plasma cilastatin concentration in patients with liver dysfunction.

drug reaction, i.e., seizure which could be related to the high dose of imipenem.

The AUC₀₋₈s of imipenem and cilastatin showed no correlation with the total CL_{CR} (for imipenem, $r = -0.471$ and $P = 0.072$ [one-tailed test]; for cilastatin, $r = 0.158$ and $P = 0.321$ [one-tailed test]).

Interestingly, in patients with markedly elevated liver function test results (function B), CL of cilastatin was significantly lower than that in patients with normal liver function test results (function A) ($P = 0.016$). For imipenem there was no significant difference between these two groups ($P = 0.26$). Plasma concentration-versus-time curves for imipenem and cilastatin in patients with and without additional liver dysfunction are depicted in Fig. 3.

DISCUSSION

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, imipenem is eliminated by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CL_{NR} of imipenem is reduced from approximately 130 ml/min in patients with normal renal function (26, 33) to approximately 50 ml/min in patients with ESRF (3, 11). A reduction of CL_{NR} rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic data obtained for these patients have been incorporated into drug dosing tables which are used to modify pharmacotherapy in patients with renal failure (2, 32). Little information, however, is available concerning the pharmacokinetic alterations that occur in patients with ARF and under treatment with CVVH. In our patients the CLs of imipenem and cilastatin were approximately 122 and 29 ml/min, respectively, with nonrenal, nonhemofiltration clearances of 91 and 13 ml/min, respectively, and CL_{HF}s of 23 and 16 ml/min, respectively. For the CL_{NR} of imipenem, similar data have been reported by Mueller et al. (23). Their assumption of an Sc of 0.8 according to the unbound fraction of the drug in healthy subjects, however, resulted in an underestimation of CL_{HF} (13 ml/min). In this study two different equations were used to calculate the CL_{HF} of the drugs, and both led to similar results (Table 2). The CL_{HF} of imipenem accounts for approximately 20% of the

total CL, which is considerably higher than the 7% reported to have been obtained with CAVH (19). Published dose recommendations for patients with ARF treated with CAVH (4, 28) are based on an estimate of CL_{HF} and on an estimate of the CL_{NR} of the drug derived from the literature, which is normally assumed to be constant over the time of renal failure. However, applying these dose recommendations to patients with ARF and undergoing CVVH will lead to underdosing because (i) CL_{NR} in patients with ARF is considerably higher than that in patients with ESRF and (ii) CVVH clearance values exceed CAVH clearance values.

The imipenem dosage requirements in our patients ($2,111.8 \pm 493.4$ mg/24 h) greatly exceeded the recommended dosage of 1,000 mg/24 h for oligoanuric patients with infections due to intermediately resistant bacteria (11, 22, 35). It has been shown that for β -lactam antibiotics the most appropriate surrogate marker for predicting the outcome is the duration of time that the concentration in plasma exceeds the MIC (15). For more resistant organisms there is an additional concentration dependence for the observed effect (15). Although a postantibiotic effect has been reported for imipenem in vitro, the clinical significance of this effect has not been evaluated (21). Therefore, it is desirable to maintain the concentration of the antibiotic in plasma over the MIC throughout the whole dosing interval. In our patients the concentrations in plasma remained above the MIC for susceptible bacteria (4 mg/liter) for approximately 6 h after they received doses of 500 mg of each of imipenem and cilastatin. This is in accordance with the results of Przechera et al. (27). Thus, a dosing regimen of 0.5 g of each of imipenem and cilastatin four times a day seems appropriate for the treatment of susceptible bacteria in patients with ARF and undergoing CVVH. Even higher doses or more frequent dosing intervals may be needed for some patients if intermediately resistant bacteria are the cause of the infection. Underdosing with the antibiotic may cause treatment failure, prolongation of hospitalization, rising health care costs, and the emergence of resistant strains.

As has been shown in other studies (11, 19), the nonrenal elimination of cilastatin was low (13.2 ± 13.9 ml/min) in our patients, but it had remarkable variability. Consequently, clearance of drug by CVVH (16.1 ± 3.1 ml/min) became more important in overall drug elimination (65%). Cilastatin clearance during CVVH was remarkably higher than that during CAVH (4 ± 0.8 ml/min) (19), which might explain the more prolonged elimination half-life in anuric patients undergoing CAVH (19). However, even CVVH did not prevent the profound accumulation of cilastatin which led to very high levels of drug in plasma. These were particularly high in patients with an additional liver dysfunction, and the highest cilastatin values were observed in two patients who had received liver transplants. Although no evident toxicity of cilastatin has been reported so far (5, 7, 19) and was not observed in our patients, the inevitable accumulation of this drug should be regarded as undesirable, and some sort of toxicity that is not obvious cannot be ruled out. Hence, the fixed combination of the two drugs is not a favorable treatment, especially for patients with ARF, for whom higher imipenem doses are needed, and for patients with an additional liver dysfunction, in whom cilastatin accumulation is the most pronounced. In our patients the dosage of cilastatin required to reach a C_{SSav} of 12 mg/liter was 504.9 ± 235.9 mg/24 h, which was approximately one-fourth of the calculated imipenem dose. However, it is not known if cilastatin concentrations throughout the dosing interval are required to be as high as the imipenem concentrations. It is possible that even smaller doses of cilastatin may be sufficient in order to inhibit DHP I. Therefore, for patients with ARF

(treated with CVVH) and for patients with additional liver dysfunction, it seems preferable to administer an appropriate dose of each drug separately. As a practical approach, a 4:1 combination of imipenem-cilastatin might be considered. Alternatively, a carbapenem antibiotic that is not combined with a DHP inhibitor may be used.

Conclusion. Therapeutic drug monitoring of imipenem-cilastatin in patients with ARF and treated with CVVH resulted in the following observations. (i) The CL_{NR} of imipenem in patients with ARF is much less reduced than that in patients with ESRF, (ii) clearance by CVVH accounts for 20% of the total CL of imipenem and should be considered in dosing regimens, (iii) marked accumulation of cilastatin occurred, particularly in patients with additional liver dysfunction, and (iv) the dosage requirements for these patients were considerably higher than the dosages recommended by the manufacturer. The use of these published dosing recommendations may result in inadequate pharmacotherapy. The results obtained for our patients, however, require confirmation with a larger population-based study.

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